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ENVIRONMENT DIRECTORATE
JOINT MEETING OF THE CHEMICALS COMMITTEE AND THE WORKING PARTY ON CHEMICALS, PESTICIDES AND BIOCIDES

Thought-starter on the expansion of MAD to computational methods

60th Joint Meeting of the Chemicals Committee and the Working Party on Chemicals, Pesticides and Biotechnology

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The OECD Test Guidelines Programme is receiving proposals for guidelines that integrate a variety of innovative approaches to predict increasingly complex endpoints. Some new methods, for example, use *in vitro* methods in combination to predict *in vivo* endpoints. Other examples included methods that measure altered gene expression following chemical exposure and use complex predictive algorithms based on machine learning approaches to interpret the results, thereby blurring the distinction between lab-based and computationally derived data. Emerging alternative methods to predict complex apical outcomes such as impaired fertility or neurodevelopment include batteries of *in vitro* and *in silico* approaches. Inclusion of these innovative guideline approaches will thus require the development of principles for assuring robust computational aspects of methods can be reproduced with high fidelity in a quality assurance system like the GLP for test data.

The aim of this document is to receive Joint Meeting feedback and recommendations for developing a strategy to maintain harmonised approaches for chemical safety assessment and preserving the Mutual Acceptance of Data generated by innovative, state of the art scientific methods. We propose near term and longer-term options to assure countries and industries continue to benefit from the data and cost sharing under MAD.

ACTION REQUIRED: ***The Joint Meeting is invited to:***

(i) discuss the considerations described herein;

(ii) provide recommendations and feedback to the Secretariat.

1. Background

1. For the past four decades, the OECD Environment, Health and Safety Programme has been helping governments develop tools and implementation practices for chemical safety. One of the key pillars of the OECD Environment, Health and Safety Programme is the Mutual Acceptance of Data (MAD) system[1]. Under MAD, test data generated in an OECD member or adhering country following OECD Test Guidelines and according to OECD Principles of Good Laboratory Practices (GLP) shall be accepted by other member or adhering countries for purposes of assessment and other uses related to the protection of humans and the environment. By reducing duplication and creating a framework for work sharing, the MAD system saves governments and industry more than 309M Euro/year (OECD, 2019[1]).

2. The OECD is also committed to assimilating best practices and supplying policy makers with tools needed to help make decisions in an increasingly digital and data driven world ([HYPERLINK "https://www.oecd.org/going-digital/"]). To aid this transition, OECD is developing policy guidance and analyses to help realise the promises of digital transformation. This includes implementing the most state-of-the art scientific tools for evaluating chemicals safety.

3. Chemical safety evaluation has benefited from the extraordinary expansion in innovative toxicological methods and the revolution in data science. Regulators acknowledge that modern toxicology is no longer restricted to laboratory experiments, and that MAD is not limited to the experimental raw data. Indeed, many *in vitro* methods adopted as OECD Test Guidelines (*e.g.* skin irritation, skin corrosion, eye irritation) include prediction models to translate raw data into results interpretable in a given context (*i.e.* subcategories defined according to the UN Globally Harmonised System for Classification and Labelling of substances). Adoption of innovative toxicological approaches will increasingly require interpretation of raw data to be meaningful in a given regulatory context. In order for the results to be covered by MAD, OECD Test Guidelines need to be precise regarding data interpretation to limit possible diverging interpretations.

4. New *in vitro, in chemico,* and *in silico* methods are proposed for testing chemicals as stand-alone methods and to be used in combination to predict increasingly complex endpoints. To date, OECD Test Guidelines describe procedures for evaluating chemical effects using a single method. Test chemicals are added to the test system and effects are observed. However, the OECD now has proposals for Guidelines using methods in combination. Methods (*i.e.* information sources) can be combined in different ways, and thus introduce potential variability in the approaches for evaluating chemical effects and the interpretation of the resulting data. To avoid this potential variability, the OECD launched work to define the information sources and data interpretation procedures for methods used in combination to predict chemical effects on a specified endpoint (*i.e.* Defined Approaches). Because Defined Approaches fix the information sources, how

[1] The "MAD Acts" include the Decision of the Council concerning the Mutual Acceptance of Data in the Assessment of Chemicals [C(81)30/FINAL] and the Decision-Recommendation of the Council on Compliance with Principles of Good Laboratory Practice [C(89)87/FINAL]. These have been opened to non-Member adherence by the Council through its Decision on Adherence of non-Member Countries to the Council Acts related to the Mutual Acceptance of Data in the Assessment of Chemicals [[HYPERLINK "https://one.oecd.org/document/C(97)114/FINAL/en/pdf"]].

information sources are combined, and the interpretation of resulting data, any two parties using the same Defined Approach will come to the same conclusion.

5. The current Defined Approaches that are being considered for inclusion in OECD Test Guidelines include *in vitro* and *in silico* methods used in specified combinations, and data interpretation procedures are relatively simple additive or rules-based models. Other Defined Approaches that have been reviewed as Case Studies are entirely *in silico* and use complex computational data interpretation models.

6. The consideration of increasingly computational approaches for evaluating chemical safety has led to a need to clarify what types of "data" are covered under MAD. In some cases, the information sources (*e.g. in silico* predictive models) or the translation of raw data using a complex data interpretation procedure to come to a result (*e.g.* omics approaches) may not easily conform to MAD or principles of GLP, as originally conceived for animal experimental data generated in a laboratory or the field.

7. Revisions to the guidance and instruments that support MAD may be needed to assure Member Countries continue to benefit from international harmonisation of chemicals safety testing.

8. Specific considerations regarding computational methods include the following:

- The 1981 Council Decision on MAD refers to acceptance of "data" and does not explicitly specify the diversity of possible types of data covered (*e.g., in silico, in vitro, etc.*) or tests used to generate the data (*e.g.* traditional animal tests, alternative methods).
- "Computational methods" may refer to mathematical operations that are applied to raw data resulting from *in vitro* methods. In most cases, an equation or model is used to convert the raw data in order to make assessments on the safety of test chemicals (*e.g.* data interpretation procedure).
    - For example, the direct output from *in vitro* methods (*e.g.* counts of radioactivity, luminescence, light transmission) are not considered, but rather a standardised computational model is used to convert raw data to something that can be easily used for regulatory purposes (*e.g.* positive/negative; potency categories).
    - Defined Approaches take this a step further by including data interpretation procedures for the data resulting from the combination of more than one information source.
    - Currently, MAD only references "data", however, results of OECD Test Guidelines that include the data interpretation are covered by MAD.
- "Computational methods" may also refer to *in silico* approaches that predict the toxicological response, such as quantitative structure-activity relationship (QSAR) models. Methods proposed in OECD Guidelines for Defined Approaches for skin sensitisation include computational (*in silico*) methods to be used with *in vitro* data. In the future, other approaches may be proposed that do not include any (*de novo*) laboratory-derived data. However, the principles of GLP are specific to laboratory-generated data and are not relevant for *in silico* predictive methods. Another quality system may therefore be needed to assure computational data are high quality, reproducible, and accepted for regulatory decision under MAD.

2. Recent developments in countries and the OECD

9. International regulatory authorities are exploring opportunities to reduce or ban animal testing, and expand the use of non-animal methods. For example, the European Union Directive 2010/63/EU restricts the manufacture or marketing of cosmetic products that have undergone animal tests, nor can companies rely on *in vivo* data for cosmetics products imported from outside the European Union. Similar restrictions in the use of animal testing for cosmetics ingredients exist in India, Australia and Korea.

10. In December 2016, [HYPERLINK "https://www.ncadierproevenbeleid.nl/documenten/rapport/2016/12/15/ncad-opinion-transition-to-non-animal-research"] produced by the Netherlands National Committee for the Protection of Animals called for eliminating animal testing for chemical safety, food ingredients, pesticides and medicines by 2025.

11. In September 2019, the US Environmental Protection Agency [HYPERLINK "https://www.epa.gov/newsreleases/administrator-wheeler-signs-memo-reduce-animal-testing-awards-425-million-advance"] to reduce animal testing by 30% by 2025 and to completely eliminate animal testing by 2035. The directive notes that the non-animal approaches currently available allow better prediction of potential hazards than traditional animal testing. US Government funding has been dedicated to finding non-animal models for complex toxicological endpoints including developmental and reproductive toxicity and neurotoxicity.

12. An OECD project to develop a developmental neurotoxicity testing battery to address regulatory needs is underway. The project is supported by complementary activities from the Danish EPA, EFSA, and the US EPA. Neurodevelopment may be affected by a variety of complex processes and accurate prediction of adverse outcomes will involve compilation of *in vivo* and *in vitro* data from a variety of regulatory agencies, development of *in vitro* assays measuring a suite of molecular targets, and sophisticated computational approaches to integrate data in a predictive model. The resulting non-animal approach(es) may provide better mechanistic understanding of the disease process and prove to be a superior predictor of the human response when compared to the current animal toxicology test.

13. Developing alternative methods for predicting complex endpoints will also rely on more intelligent test systems. Organotypic 2D and 3D cell culture systems are capable of expressing physiological biomarkers of organ systems function and are robust human tissue mimetics. In 2016, the US National Institutes of Health established three Tissue Chip Testing Centres to test and validate microphysiological tissue chips ([HYPERLINK "https://ncats.nih.gov/tissuechip/projects/centers"]). The validation effort aims to adhere to OECD standards for method validation, guidance for non-guideline methods, and guidance documents published by other agencies regarding validation of alternative methods for regulatory application. A similar effort has been undertaken with the 2017 European Union ORCHID (Organ-on-Chip development) project involving seven European research institutions ([HYPERLINK "https://h2020-orchid.eu/"]).

14. It will likely be several years before organotypic cell culture models and tissue chip technologies are proposed for inclusion in OECD Test Guidelines, but guidelines proposed in the interim are expected to include many of the toxicological and computational advances of the past decade. In order for the OECD Test Guidelines Programme and

Mutual Acceptance of Data to remain relevant, there need to be instruments that anticipate uptake of these new technologies for chemical safety testing.

3. Proposed path forward to adapt OECD instruments

15. The Test Guidelines Programme recognises that Member Countries will propose guidelines to assess the safety of chemicals that are aligned with initiatives to reduce animal testing and include more physiologically sophisticated, human-relevant models. The goal of this proposal is to ensure that results of future OECD Test Guidelines can continue to be covered by MAD.

16. The OECD strives to keep pace with the most state-of-the-art scientific methods for use in regulatory decision-making. As *in silico* and computational methods evolve to include artificial intelligence, such as machine learning approaches and designing of artificial neural networks, more explicit policies to ensure digital data integrity can be developed in accordance with the [HYPERLINK "https://www.oecd.org/going-digital/ai/principles/"] but are currently beyond the scope of this document.

17. The current wording of the Council Act on MAD allows for sufficient flexibility to cover DAs. For the near term, minor updates to existing documents that support MAD may accommodate novel laboratory and computational data approaches. For future clarity and in anticipation of increasing complex approaches, further revisions to OECD legal instruments and guidance on best practices may be appropriate.

Instruments and guidance that could be adapted or developed

The Council Act on the Mutual Acceptance of Data in the Assessment of Chemicals

Near term

18. Existing language in Part 1.1 of the 1981 Council Decision

> "*…data generated in the testing of chemicals in an OECD Member country in accordance with OECD Test Guidelines and OECD Principles of Good Laboratory Practice shall be accepted in other Member countries for purposes of assessment and other uses relating to the protection of man and the environment*".
>
> could be amended as follows:
>
> "*…**(in chemico, in silico, in vitro, in vivo, etc.)** data generated in the **standardised evaluation or** testing of chemicals in an OECD Member country in accordance with OECD Test Guidelines and OECD Principles of Good Laboratory Practice shall be accepted in other Member countries for purposes of assessment and other uses relating to the protection of man and the environment*".

19. *In silico* data would still be required to adhere to validation standards, discussed below, that are intended to assure quality of computational data (equivalent to the aims of GLP for laboratory data).

Longer term

20. The 1981 Council Decision could be updated to explicitly include language regarding principles for computational data, analogous to Good Laboratory Practices for lab-derived data (*e.g.* "Good Computational Practices").

Development of quality assurance standards for computational data

21. Current OECD guidance on validation of *in silico* models for regulatory purposes provides a set of principles (GD N° [HYPERLINK "http://www.oecd.org/officialdocuments/publicdisplaydocumentpdf/?cote=env/jm/mono(2004)24&doclanguage=en"] and [HYPERLINK "http://www.oecd.org/officialdocuments/publicdisplaydocumentpdf/?cote=env/jm/mono(2007)2&doclanguage=en"]), but no formalised process for acceptance of predictions. There are also existing OECD formats for documentation than can be used to report *in silico* models and predictions.

22. In 2018, the OECD convened a [HYPERLINK "https://one.oecd.org/document/ENV/JM/HA/M(2018)8/en/pdf"] to discuss *in silico* data produced as part of Defined Approaches and potentially covered under MAD. Participants suggested that GLP could not be applied to QSAR [[HYPERLINK "https://one.oecd.org/document/ENV/JM/HA/M(2018)8/en/pdf"]] because, *inter alia*, GLP principles apply to laboratory or field testing. However, documentation quality standards already exist for QSARs (*e.g.* QSAR Prediction Reporting Formats (QPRF) and QSAR Model Reporting Format (QMRF)).

23. The groups provided recommendations on issues related to validation, transparency and reproducibility for *in silico* models and predictions, some of which could be implemented in the near-term.

Near-term

24. The following recommendations from the November 2018[HYPERLINK "https://one.oecd.org/document/ENV/JM/HA/M(2018)8/en/pdf"] could be implemented as a first step of developing "Good Computational Practices":

a. The QSAR Model Reporting Format (QMRF) can be used to document and describe the *in silico* model.

b. A detailed description of how the model was run can be included in the Test Guideline to remove variability, expert judgement, and assure predictions are reproducible.

c. The QSAR Prediction Reporting Format (QPRF) can be used to document the prediction resulting from *in silico* models.

Longer term

25. The Expert Groups recognised during the meeting and in discussions that followed with the Working Party on Hazard Assessment that the development of an assessment framework for *in silico* models predictions would be helpful. Currently no country/organisation has come forward to take the lead on such a project, due to lack of resources. .